97. The method of claim 60, wherein the adenovirus vector is an Ad1, Ad2, Ad5 or Ad6 vector.

98. The method of claim 60, wherein the adenovirus vector is administered to the tumor by injection of vector intravenously or intrathecally.

99. The method of claim 60, wherein the adenovirus vector is administered to the tumor by direct injection of the tumor.

100. The method of claim 60, wherein the patient is passively immunized.

REMARKS

I. Claims in the Case/Claim Amendments

Claims 1, 2, 4, 10, and 45-59 have been cancelled without prejudice, claims 5, 11-13 and 28-44 have been amended, and claims 60-100 have been added. Claims 5, 11-14, 20-22, 24, 33-44 and 60-100 are currently pending.

Claim 5 has been placed into independent format and should be in condition for allowance.

The dependencies of claims 11, 12, 29, 30, 31, 33 and 39 have been changed.

Claim 13 has been amended to place it into independent form by introducing language from claim 10 as well as additional language to more clearly specify what is intended by the phrase "overexpresses an adenovirus death protein." The claim now indicates that ADP expression is defined as "overexpression relative to a control adenovirus vector that has the E3 structure of *dl*309 but otherwise has the same genetic structure as the overexpressing vector."

Support for this can be found in the specification, for example, in Figure 2 and in the specification at pages 24-25. Here, the ADP-overexpressing vectors KD1 and KD3 are

compared to *dl*01/07 (page 24, lns 13-15) and shown to have a much higher expression of ADP than dl01/07 (see Figure 2). This is appropriate because KD1, KD3 and dl01/07 all have the 01/07 mutations in their E1 region that lead to tumor selective growth, yet the overexpressing vectors KD1 and KD3 have deletions in their E3 regions that give rise to the overexpression whereas dl01/07 has an E3 region that is identical to the E3 region of *dl*309. The mutation in the E3 region of *dl*309 does not lead to overexpression of ADP compared to wild type Ad5; that the mutation does not affect expression of ADP is shown by Doronin et al., 2003 (copy enclosed). It is not scientifically appropriate to compare KD1 and KD3 to *dl*309 because, as shown in Figure 3 of the specification, the E1A mutation in KD1 and KD3 leads to a delay in expression of adenovirus late genes, *i.e.* late proteins, as compared viruses such as Ad5 and *dl*309 which have wild type E1A. Since ADP is predominantly a late gene, its expression will also be delayed by the E1A mutation.

To state our point again, KD1 and KD3 should be compared to *dl*01/07 because all three viruses have the same E1A deletion which delays the infection process. Although KD1 and KD3 should be compared to *dl*01/07, the fact that the western blot data in Fig. 2 of the specification indicate that KD1 and KD3 overexpress ADP compated to *dl*309 at 24 h p.i. speaks even more emphatically to the conclusion that KD1 and KD3 overexpress ADP.

Similarly, a comparison is made between GZ1/GZ3 and *dl*309 (page 24, lines 15-17), and GZ1/GZ3 are shown to have a much higher expression of ADP that *dl*309 (see Figure 2). This comparison is similarly appropriate in light of the fact that all three of GZ1, GZ3 and *dl*309 are wild-type with respect to their E1 regions, whereas GZ1 and GZ3 have modified E3/ADP regions and *dl*309 has a deletion of most of the E3B region but is for the most part wild-type in

its E3A region. It should be noted that *dl*309 (and therefore *dl*01/07) has an insertion of foreign DNA in place of the deleted E3 region.

Claims 28-31 and 33-44 have been amended to change them into dependent method claims from now independent claim 13.

Additionally, claim 28 now recites that the vector is either replication-defective (see specification page 11, lines 30-33) or which is replication-restricted to dividing cells (see specification beginning at page 11, line 34).

Claim 32 has been amended and is now directed to determining overexpression by western blot (See Figure 2), by cell lysis, *e.g.*, using the plaque assay (see specification in Example 2) or by a cell spreading assay (see Example 2).

Claim 40 has been amended to remove reference to the 6.7 K and 12.5K E3 proteins.

New claim 60 is directed to a method of promoting death of a neoplastic cell in a patient by administering an adenovirus that is replication-competent in neoplastic cells and that expresses ADP, wherein the adenovirus one or more of four possible structural features represented by element a), b) c) and/or d). Support for element a), and claims 68-69, can be found in the specification, for example, at page 13, lns 4-5; support for element b), and claim 72, can be found, for example, at page 12, lns 33-35; and support for elements c) and d) can be found, for example, at page 13, lns 2-4, 5-8.

Support for claims 70-71 can be found at page 13, lns 5-8.

Support for claim 76-77 can be found in the specification, for example, at pages 11-12, 16-17, and various of the examples.

Support for claims 78-79 can be found at page 16, lns 1-33 and in Example 1 which describes the construction of KD1 and KD3.

Support for claims 80-96 can be found in the specification at page 6, lns 15-22, and page 16, ln 34, through page 18, ln 30.

Support for claims 97-100 can be found at pages 18-20.

New claims that have not been mentioned in the foregoing support section are derived from claims currently and/or previously of record.

II. Interview

The Examiner kindly granted Applicants' representative a personal interview, which was held on April 24, 2003. In connection with that interview, a proposed agenda was made of record. During the interview the undersigned Applicants' representative and the Examiner briefly discussed ways to overcome the 112, first paragraph, rejections and the sufficiency of the 131 declaration to overcome Little/Henderson as described in the agenda.

III. Reintroduction of Claims

The Examiner withdrew claims 28-31 on the basis that these claims were directed to a non-elected invention, stating that there is no allowable generic or linking claim. Applicants have herein reintroduced these claims, converted them to method claims, and they now depend from what is considered to be an allowable base claim, claim 13.

IV. Specification

Table 1 has been amended as suggested in the subject Action to correct an obvious typographical error, by changing "Ad5 bp 27858-2760" to Ad5 bp 27858-27860" for each of KD1, GZ1 and KD1-SPB. That this is an obvious typographical error is evident from the fact that in each case the deletion referred to is replaced by the trinucleotide sequence TAA, indicating that the deleted region was only 3 nucleotides in length.

V. Claim Objections

At the top of page 3 of the Action there are objections made to claims 56-58. In that these claims are no longer pending, the objections are moot.

VI. Rejection of Claims Under 35 U.S.C. §112, First Paragraph

The Action next rejects claims 40, 45-55 and 59, taking the position that the specification only provides support for attenuation of one or more of gp19K, RIDα, RIDβ or 14.7K, but not 6.7K or 12.5K standing alone.

Applicants have amended the claims in a manner that is believed to address the Examiner's concerns.

Claims 45 and 51 are no longer pending.

VII. Rejection of Claims Under 35 U. S.C. §112, Second Paragraph

The Action next rejects claims 1, 2, 4, 10-14, 21, 22, 24 and 32-44 under 35 U.S.C. §112, Second Paragraph for reasons stated in the Action.

In response, Applicants reiterate that it is their belief and experience, as stated in the specification, that the removal of an E3 region splice site will generally result in an adenovirus that overexpresses ADP. This is a general rule, likely not an absolute rule. For example, there can be other genetic factors present in the vector that can, at the same time, down-regulate ADP expression. For example, it appears evident from Figure 2 that the 01/07 E1 mutation effects a down regulation of ADP expression in the over-expressing vector (*e.g.*, KD1) as compared to ADP over-expressing vectors that do not contain the 01/07 E1 mutation (*e.g.*, GZ1). Thus, the ultimate vector may appear to have no increased ADP expression due to concomitant overexpression and underexpression of ADP. Furthermore, it is known that *dl*309 expresses generally wild-type levels of ADP (Doronin *et al.*, 2003), even though it has certain splice sites

removed from its E3B region. It is postulated that the reason for this is due to the presence of foreign DNA that has been inserted into the deleted E3 regions.

To address the foregoing concerns, claim 13 has been amended as explained in Section I above to clarify what is intended by the phrase "ADP overexpression."

VIII. Rejection of Claims Over Tollefson and Tollefson/Bett

The Action next rejects various of the claims as either anticipated by Tollefson or obvious over the combination of Tollefson and Bett *et al.*

In response it is noted that therapeutic method claim 13 was not found to be either anticipated or obvious over these references in that the references fail to teach human therapy. Accordingly, all of the current claims are now directed to human therapy and thus are not anticipated or obvious over these references.

IX. Rejection of Claims Over Henderson and Little

The Action next rejects various claims as anticipated by or obvious over one or both of the Henderson and Little patents, alone or in combination with Freytag *et al.* To make out the rejection, the Action relies on the CN751 vector described, for example, in Example 6 of both patents. Applicants respectfully traverse.

It is clear from the description in Little and Henderson that CN751 is a serotype 5 adenovirus that has its E3 region removed and replaced with some non-contiguous coding sequences from the adenovirus serotype 2 E3 region that consists of the ADP coding sequence plus some flanking sequences, and the Y-leader plus some flanking sequences. See, *e.g.*, col. 48, lines 4-46, particularly at lines 15-20 wherein it is stated that preparation of CN751 started with an E3-deleted platform from Ad5 into which was placed and Ad2 ADP gene. So, CN751 is intended to reflect the general concept of an adenovirus vector where much of the E3 region has

been deleted and the ADP gene maintained. This general concept of "maintaining" an ADP coding region in discussed with respect to Figure 5 at, for example, col. 27 beginning at line 33. Figure 5 also appears to a deleted E3 region that maintains an ADP coding region.

It is worth noting that CN751, and studies employing CN751, are not described in the provisional priority application of Little/Henderson, nor are any animal studies employing CN751. Applicants have enclosed a copy of 60/039,762 (Henderson priority) and 60/039,597 (Little priority) for the Examiner's review. While there does appear to be discussion of E3-modified ADP expressing vectors (see, *e.g.*, Figure 5 and Example 4 of 60/039,762), these figures depict **plasmids not adenoviruses**, there does not appear to be a disclosure of any animal studies or any ADP expression using such plasmids. Thus, to the extent that the Examiner is relying on CN751 as prior art, a description of CN751 first appeared in the Henderson/Little application filed March 2, 1998.

In addressing the rejection, we first incorporate by reference all of the arguments related in earlier responses regarding the failure of the Action to make out a *prima facie* rejection.

That aside, Applicants point out that the law is clear that an antedating 131 declaration need only show so much as the prior art discloses. See, *e.g.*, *In re Stempel*, 113 U.S.P.Q. 77 (CCPA 1957).

In Applicants' earlier submitted 131 declarations, two facts are quite clear. First, vector KD1 was prepared prior to the March 3, 1997 priority date of Henderson/Little. (See inventors' 131 declaration filed 1/6/03, particularly paragraph 6 and associated exhibits). The KD-1 vector included what appears to be an almost identical E3 region to that of Henderson/Little, where the E3 region was deleted and replaced with an ADP coding region. (See, *e.g*, third bullet point from top of page 3 of inventors' 131 declaration filed 1/6/03). As explained in paragraph 6 of

the declaration, this vector was fully constructed by transfections carried out prior to March 3, 1997. Secondly, KD1 was shown to overexpress ADP in various experiments conducted between 5/9/97 and 5/23/97 (Declaration page 8) and between 5/13/97 and 6/2/97 (Declaration pages 8-9). Furthermore, a Western blot carried out in December 1997 further confirmed KD1 overexpression of ADP (Declaration, bottom of page 9).

In January of 1998, KD1 and KD3 were successfully tested in animal models and shown to suppress the growth of A549 tumors in nude mice. (See page 7, first full paragraph, Declaration dated December 20, 2001, and particularly Exhibit D thereto).

Thus, it is submitted that the present Applicants carried out in the United States studies that demonstrate the reduction to practice of an ADP-overexpressing adenovirus and successful demonstration of tumor growth suppression prior to the March, 1998, effective filing date of the CN751 description in Little/Henderson. Thus, under the doctrine of *In re Stempel* discussed above, it is submitted that the Little/Henderson references have been antedated inasmuch as the 131 showing is at least commensurate in scope with that found in the March 1997 and March 1998 respective filing dates of the Henderson/Little patents.

The Action unnecessarily focuses on the scope of showing and implies, contrary to the clear holding in *Stempel*, that the Applicants must somehow show a reduction to practice of the entire genus prior to Little/Henderson. The Action's position is, as noted, contrary to *Stempel* and a long line of successor cases. For example, in *In re Hostettler*, 148 U.S.P.Q. 514 (CCPA 1966), the court was adamant in reversing the PTO on this very point:

> Rule 131 requires applicant to make oath to facts showing a completion "of the invention." That requirement does not mean affiant must show a reduction to practice of every embodiment of the invention. Nor is that requirement coextensive with the amount of disclosure necessary to support a claim under 35 USC 112.

148 U.S.P.Q. at 516.

Furthermore, even if the Examiner concludes that Applicants' showing is not of precisely the same vector as CN751, such a finding should in no way undermine Applicants claim to priority. The fact is, if there are differences, the differences are not relevant to the fundamental issue of who first demonstrated reduction to practice of the central concept of expressing or overexpressing ADP from a recombinant adenovirus for the purposes of cancer therapy. That showing has clearly been made by the present Applicants. Furthermore, the case law again strongly supports our position. For example, *In re Clarke*, 148 U.S.P.Q. 665 (CCPA 1966), presented the situation where the 131 affidavit described embodiments that were similar to but distinct from the disclosure contained in the reference at issue. In reversing the Board and the examiner, the court observed that:

> We believe that Stempel ... is not limited to the fact situations where the inventor can show priority as to the identical compound described in the reference. It seems that in an appropriate case as applicant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in that art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference.

148 U.S.P.Q. at 670. Here, the fact that Applicants' earlier-reduced-to-practice KD1 included the 01/07 E1 mutation in addition to the upregulating ADP/E3 mutations should thus in no way detract from the ability of KD1 to effectively antedate a reference teaching the ADP/E3 mutations without the 01/07 mutations. Stated another way, KD1 would appear to anticipate or at least obviate CN751, at least to the extent that both are principally concerned with vectors that express ADP as the operative lytic agent.

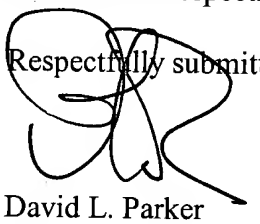
For each of the foregoing reasons, the Examiner is requested to reconsider and withdraw the pending rejections over Henderson and Little.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn because they are in condition for allowance. At the very least, Applicants request entry of these amendments in order to place the case in better form for an appeal.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3055 is respectfully requested.

Respectfully submitted,



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Date: June 19, 2003

AMENDMENTS TO TABLE 1

Table 1: Description of mutations in viruses:

Virus	RNA REGION			
	E1	VA	E3	E4
*dl*1101/1107	*dl*1101: deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	From *dl*309 deletion of Ad5 bp 28597-28602; deletion-substitution Ad5 bp 3005-30750, insert 642 bp DNA of unknown origin	wild type
KD1	*dl*1101: deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	deletion of Ad5 bp 27858-27860, TAA inserted; deletion of Ad5 bp 27982-28134; deletion of Ad5 bp 28395-29397, insert CCTTAATTAAA; deletion of Ad5 bp 29783-30883, insert TTAATTAAGG	wild type
KD2	*dl*1101: deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	*dl*309 background, gp19K mutated deletion of Ad5 bp 28597-28602; deletion-substitution Ad5 bp 3005-30750, insert 642 bp DNA of unknown origin; deletion of Ad5 bp 28788-28789, insert TTAATTAA	wild type
KD3	*dl*1101: deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	deletion of Ad5 bp 28598-29397; deletion of Ad5 bp 29783-30469	wild type
GZ1	wt	wild type	deletion of Ad5 bp 27858-27860, TAA inserted; deletion of Ad5 bp 27982-28134; deletion of Ad5 bp 28395-29397, insert CCTTAATTAAA; deletion of Ad5 bp 29783-30883, insert TTAATTAAGG	wild type

GZ3	wild type	wild type	deletion of AD5 bp 28598-29397; deletion of Ad5 bp 29783-30469	wild type
*dl*1101/1107-SPB	*dl*1101: deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	From *dl*309 deletion of Ad5 bp 28597-28602; deletion-substitution Ad5 bp 3005-30750, insert 642 bp DNA of unknown origin	E4 promoter deletion-substitution: deletion of Ad5 bp 35623-35775, insert SP-B 500 promoter flanked by Bst1 107I sites
KD1-SPB	dl*1101:* deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	deletion of Ad5 bp 27848-27860, TAA inserted; deletion of Ad5 bp 27982-28134; deletion of Ad5 bp 28395-29397, insert CCTTAATTAAA; deletion of Ad5 bp 29783-30883, insert TTAATTAAGG	E4 promoter deletion-substitution: deletion of Ad5 bp 35623-35775, insert SP-B 500 promoter flanked by Bst1 107I sites
KD3-SPB	*dl*1101: deletion of Ad5 bp 569-634 *dl*1107: deletion of Ad5 bp 890-928	From *dl*309 deletion of Ad5 bp 10594-10595	deletion of Ad5 bp 28598-29397; deletion of Ad5 bp 29783-30469	E4 promoter deletion-substitution: deletion of Ad5 bp 35623-35775, insert SP-B 500 promoter flanked by Bst1 107I sites

CLAIM AMENDMENTS

~~1. A recombinant adenovirus vector which is replication-competent in neoplastic cells and which overexpresses an adenovirus death protein.~~

~~2. The adenovirus vector of claim 1 wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.~~

~~4. The recombinant adenovirus vector of claim 2, wherein the recombinant adenovirus lacks expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.~~

5. (Amended) A recombinant adenovirus that ~~The recombinant adenovirus vector of claim 4, wherein the recombinant adenovirus~~ comprises SEQ ID NO:1 or SEQ ID NO:2.

~~10. A method for promoting death of a neoplastic cell comprising contacting the neoplastic cell with an adenovirus vector, wherein~~

~~(a) at least one adenoviral vector is introduced into the neoplastic cell, and~~

~~(b) said adenovirus vector is replication-competent in neoplastic cells and overexpresses an adenovirus death protein.~~

11. (Amended) The method of claim 13~~10~~ wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

12. (Amended) The method of claim 13~~11~~, wherein the adenovirus vector comprises a recombinant adenovirus lacking expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.

13. (Amended) A method for promoting death of a neoplastic cell comprising contacting the neoplastic cell with an adenovirus vector~~The method of claim 12~~, wherein the neoplastic cell

is contained in a tumor in a patient and the contacting step comprises administering the adenovirus vector to neoplastic cells of the tumor, and further wherein:

(a) at least one adenoviral vector is introduced into the neoplastic cell, and

(b) said adenovirus vector is replication-competent in neoplastic cells and overexpresses an adenovirus death protein, wherein overexpression is defined as overexpression relative to a control adenovirus vector that has the E3 structure of dl309 but otherwise has the same genetic structure as the overexpressing vector.

28. (Amended) The method of claim 13, wherein the ~~A recombinant adenovirus vector, wherein said~~ adenovirus vector ~~(a)~~ is replication defective, or it is replication-restricted to dividing cells or neoplastic cells.~~, (b) contains a mutation in the E1A gene, and (c) overexpresses an adenovirus death protein.~~

29. (Amended) The ~~recombinant~~ method of claim 28,~~adenovirus vector of claim 28~~1 wherein the adenovirus vector comprises a mutation in an E1A gene that renders the adenovirus incapable of expressing an E1A viral protein which binds the pRB and the p300/CBP proteins.

30. (Amended) The method of claim 28, ~~recombinant adenovirus of claim 28~~1 wherein an E4 promoter of said recombinant adenovirus vector is substituted with a promoter, which is activated ~~only~~ in neoplastic cells.

31. (Amended) The method of claim 30, ~~recombinant adenovirus of claim 30~~ wherein the promoter, which is activated ~~only~~ in neoplastic cells, is the surfactant protein B ("SPB") promoter.

32. (Amended) The method of claim 28, wherein the overexpression relative to a control virus is detectable by western blot, cell lysis or by a cell spreading assay.~~The recombinant adenovirus of claim 1 which comprises a polynucleotide that encodes an E3-12.5K protein.~~

33. (Amended) The method of claim 13 ~~recombinant adenovirus vector of claim 28~~1, wherein the recombinant adenovirus lacks expression of at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K.

34. (Amended) The method of claim ~~recombinant adenovirus vector of claim~~ 33, wherein the recombinant adenovirus lacks expression of the gp19K protein.

35. (Amended) The method of ~~recombinant adenovirus vector of~~ claim 33, wherein the recombinant adenovirus lacks expression of the RIDα protein.

36. (Amended) The method of claim ~~recombinant adenovirus vector of~~ claim 33, wherein the recombinant adenovirus lacks expression of the RIDβ protein.

37. (Amended) The method of ~~recombinant adenovirus vector of~~ claim 33, wherein the recombinant adenovirus lacks expression of the 14.7K protein.

38. (Amended) The method ~~recombinant adenovirus vector~~ of claim 33, wherein the recombinant adenovirus lacks expression of the gp19K, RIDα, RIDβ and 14.7K proteins.

39. (Amended) The method ~~recombinant adenovirus vector~~ of claim 28~~1~~, wherein the recombinant adenovirus comprises a deletion in the E3 region that removes a splice site for any of the E3 mRNAs.

40. (Amended) The method of claim 13~~recombinant adenovirus vector of claim 1~~, wherein the recombinant adenovirus comprises at least one deletion in the E3 region, wherein the at least one deletion comprises a sequence that encodes at least one E3 protein, wherein the protein is selected from the group consisting of gp19K, RIDα, RIDβ, and 14.7K~~, 6.7K and 12.5K~~.

41. (Amended) The method ~~recombinant adenovirus vector~~ of claim 40, wherein the at least one deletion comprises a sequence that encodes the gp19K, RIDα, RIDβ and 14.7K proteins.

42. (Amended) The method ~~recombinant adenovirus vector~~ of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 6.7K protein.

43. (Amended) The method ~~recombinant adenovirus vector~~ of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 12.5K protein.

44. (Amended) The method ~~recombinant adenovirus vector~~ of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 6.7K and 12.5K proteins.

~~45. A recombinant adenovirus vector, wherein said vector~~

~~(a) lacks expression of at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K; and~~

~~(b) comprises a gene that encodes ADP.~~

~~46. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the gp19K protein.~~

~~47. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the RIDα protein.~~

~~48. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the RIDβ protein.~~

~~49. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the 14.7K protein.~~

~~50. The recombinant adenovirus vector of claim 45, wherein the vector lacks expression of the gp19K, RIDα, RIDβ and 14.7K proteins.~~

~~51. A recombinant adenovirus vector, wherein said vector comprises~~

~~(a) at least one deletion in the E3 region, wherein the at least one deletion comprises a sequence that encodes at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K; and~~

~~(b) a gene that encodes ADP.~~

~~52. The recombinant adenovirus vector of claim 51, wherein the at least on deletion comprises a sequence that encodes the gp19K, RIDα, RIDβ, and 14.7K proteins.~~

~~53. The recombinant adenovirus vector of claim 51, wherein the at least one deletion further comprises a sequence that encodes the 6.7K protein.~~

~~54. The recombinant adenovirus vector of claim 51, wherein the at least one deletion further comprises a sequence that encodes the 12.5K protein.~~

~~55. The recombinant adenovirus vector of claim 51, wherein the at least one deletion further comprises a sequence that encodes the 6.7K and 12.5K proteins.~~

~~56. The recombinant adenovirus vector of claim 38, wherein the recombinant adenovirus lacks expression of the 6.7K protein.~~

~~57. The recombinant adenovirus vector of claim 38, wherein the recombinant adenovirus lacks expression of the 12.5K proteins.~~

~~58. The recombinant adenovirus vector of claim 38, wherein the recombinant adenovirus lacks expression of the 6.7K and 12.5K proteins.~~

~~59. The recombinant adenovirus of claim 51, wherein the at least one deletion comprises a splice site for any of the E3 mRNAs.~~

PENDING CLAIMS FOLLOWING ENTRY OF AMENDMENTS

5. (Amended) A recombinant adenovirus that comprises SEQ ID NO:1 or SEQ ID NO:2.

11. (Amended) The method of claim 13 wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

12. (Amended) The method of claim 13, wherein the adenovirus vector comprises a recombinant adenovirus lacking expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.

13. (Amended) A method for promoting death of a neoplastic cell comprising contacting the neoplastic cell with an adenovirus vector, wherein the neoplastic cell is contained in a tumor in a patient and the contacting step comprises administering the adenovirus vector to neoplastic cells of the tumor, and further wherein:

(a) at least one adenoviral vector is introduced into the neoplastic cell, and

(b) said adenovirus vector is replication-competent in neoplastic cells and overexpresses an adenovirus death protein, wherein overexpression is defined as overexpression relative to a control adenovirus vector that has the E3 structure of *dl*309 but otherwise has the same genetic structure as the overexpressing vector.

14. The method of claim 13, further comprising the step of passively immunizing the patient against the recombinant adenovirus.

15. The method of claim 14, wherein the recombinant adenovirus comprises SEQ ID NO:1 or SEQ ID NO:2.

20. The method of claim 13, further comprising treating the tumor with radiation.

21. The method of claim 20 comprising administering more than one distinct type of recombinant adenovirus to the tumor and treating the tumor with radiation, wherein at least one recombinant adenovirus is replication-defective.

22. The method of claim 13, further comprising treating the tumor with chemotherapy.

24. The method of claim 13, further comprising administering to the tumor one or more replication-defective adenoviruses, wherein each replication-defective adenovirus expresses an anti-cancer gene product, and wherein the recombinant adenovirus facilitates the spread of the replication-defective adenovirus in the tumor.

28. (Amended) The method of claim 13, wherein the adenovirus vector is replication defective, or it is replication-restricted to dividing cells or neoplastic cells.

29. (Amended) The method of claim 28, wherein the adenovirus vector comprises a mutation in an E1A gene that renders the adenovirus incapable of expressing an E1A viral protein which binds the pRB and the p300/CBP proteins.

30. (Amended) The method of claim 28, wherein an E4 promoter of said recombinant adenovirus vector is substituted with a promoter, which is activated in neoplastic cells.

31. (Amended) The method of claim 30, wherein the promoter, which is activated in neoplastic cells, is the surfactant protein B ("SPB") promoter.

32. (Amended) The method of claim 28, wherein the overexpression relative to a control virus is detectable by western blot, cell lysis or by a cell spreading assay.

33. (Amended) The method of claim 13, wherein the recombinant adenovirus lacks expression of at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K.

34. (Amended) The method of claim 33, wherein the recombinant adenovirus lacks expression of the gp19K protein.

35. (Amended) The method of claim 33, wherein the recombinant adenovirus lacks expression of the RIDα protein.

36. (Amended) The method of claim claim 33, wherein the recombinant adenovirus lacks expression of the RIDβ protein.

37. (Amended) The method of claim 33, wherein the recombinant adenovirus lacks expression of the 14.7K protein.

38. (Amended) The method of claim 33, wherein the recombinant adenovirus lacks expression of the gp19K, RIDα, RIDβ and 14.7K proteins.

39. (Amended) The method of claim 28, wherein the recombinant adenovirus comprises a deletion in the E3 region that removes a splice site for any of the E3 mRNAs.

40. (Amended) The method of claim 13, wherein the recombinant adenovirus comprises at least one deletion in the E3 region, wherein the at least one deletion comprises a sequence that encodes at least one E3 protein, wherein the protein is selected from the group consisting of gp19K, RIDα, RIDβ, and 14.7K.

41. (Amended) The method of claim 40, wherein the at least one deletion comprises a sequence that encodes the gp19K, RIDα, RIDβ and 14.7K proteins.

42. (Amended) The method of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 6.7K protein.

43. (Amended) The method of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 12.5K protein.

44. (Amended) The method of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 6.7K and 12.5K proteins.

60. A method for promoting death of a neoplastic cell contained in a tumor in a patient, the method comprising administering to the tumor an adenovirus vector that is replication-competent in neoplastic cells and expresses ADP, wherein:

a) the ADP is expressed from an ADP coding sequence positioned under the control of a promoter other than the endogenous promoters for ADP;

b) the adenovirus vector comprises a deletion in the E3 region that removes a splice site for an E3 mRNA;

c) the ADP is expressed from an ADP coding sequence flanked by a pre-mRNA splicing and cleavage/polyadenylation signal other than the pre-mRNA splicing and cleavage/polyadenylation signal normally associated with the ADP gene, and/or

d) the ADP is expressed from an ADP coding sequence that is positioned downstream of the coding sequence for another adenovirus mRNA, together with a sequence on the 5' side of the ADP coding sequence that allows for internal initiation of translation of ADP.

61. The method of claim 60 wherein the ADP comprises the sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

62. The method of claim 60, further comprising the step of passively immunizing the patient against the recombinant adenovirus.

63. The method of claim 62, wherein the recombinant adenovirus comprises SEQ ID NO:1 or SEQ ID NO:2.

64. The method of claim 60, further comprising treating the tumor with radiation.

65. The method of claim 64 comprising administering more than one distinct type of recombinant adenovirus to the tumor and treating the tumor with radiation, wherein at least one recombinant adenovirus is replication-defective.

66. The method of claim 60, further comprising treating the tumor with chemotherapy.

67. The method of claim 60, further comprising administering to the tumor one or more replication-defective adenoviruses, wherein each replication-defective adenovirus expresses an anti-cancer gene product, and wherein the recombinant-competent adenovirus facilitates the spread of adenoviruses in the tumor.

68. The method of claim 60, wherein the ADP is expressed from an ADP coding sequence positioned under the control of promoter other than the endogenous promoters for ADP.

69. The method of claim 68, wherein the ADP coding sequence is positioned under the control of a promoter that is exogenous to adenovirus.

70. The method of claim 60, wherein the ADP coding sequence is positioned behind a coding sequence for another adenovirus mRNA together with a sequence on the 5' side of the ADP coding sequence that allows for internal initiation of translation of ADP.

71. The method of claim 70, wherein the sequence on the 5' side of the ADP coding sequence that allows for internal initiation of translation of ADP is an Ad tripartite leader or a viral internal ribosome initiation sequence.

72. The method of claim 60, wherein the adenovirus vector comprises a deletion in the E3 region that removes a splice site for an E3 mRNA.

73. The method of claim 72, wherein the adenovirus vector lacks expression of at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ, and 14.7K.

74. The method of claim 73, wherein the adenovirus vector lacks expression of each of gp19K, RIDα, RIDβ, and 14.7K.

75. The method of claim 74, wherein the adenovirus additionally lacks expression of the E3 6.7K and 12.5K proteins.

76. The method of claim 60, wherein the adenovirus vector is replication-defective.

77. The method of claim 76, wherein the adenovirus vector is replication-restricted to neoplastic cells.

78. The method of claim 60, wherein the adenovirus vector comprises a mutation in its E1 region.

79. The method of claim 78, wherein the adenovirus vector comprises a 1101/1107 mutation in its E1A coding region.

80. The method of claim 60, wherein the adenovirus vector comprises an adenoviral gene essential for replication positioned under the control of a tissue specific or tumor specific promoter.

81. The method of claim 80, wherein the adenovirus vector comprises an E4 gene positioned under the control of a tissue specific promoter.

82. The method of claim 80, wherein the promoter is a transcriptional regulatory element, a prostate specific antigen promoter, a human alpha-lactalbumin promoter, a mammoglobin promoter, a surfactant protein B promoter, a factor VII promoter, or a survivin promoter.

83. The method of claim 60, wherein the adenovirus vector comprises an adenoviral gene essential for replication under the control of an inducible promoter.

84. The method of claim 83, wherein the inducible promoter is a metallothionein promoter, a glucocorticoid promoter, a tetracycline response promoter or a heat shock promoter.

85. The method of claim 60, wherein the adenovirus vector further comprises a coding region for an anticancer gene product.

86. The method of claim 85, wherein the anticancer gene product is an apoptosis-promoting agent.

87. The method of claim 86, wherein the apoptosis-promoting agent is a pro-apoptotic member of the BCL-2 family.

88. The method of claim 86, wherein the anticancer gene product is an antisense molecule that blocks expression of an anti-apoptotic member of the BCL-2 family.

89. The method of claim 85, wherein the anticancer gene product is an immunoregulatory molecule.

90. The method of claim 89, wherein the immunoregulatory molecule is a cytokine.

91. The method of claim 90, wherein the cytokine is tumor necrosis factor, Fas/Apo1/CD95 ligand, tumor necrosis factor related apoptosis inducing ligand, an interleukin, macrophage activating factor or interferon γ.

92. The method of claim 85, wherein the anticancer gene product is an angiogenesis inhibitor.

93. The method of claim 92, wherein the angiogenesis inhibitor is endostatin or angiostatin.

94. The method of claim 85, wherein the anticancer gene product is a toxin.

95. The method of claim 94, wherein the toxin is ricin or lymphotoxin.

96. The method of claim 85, wherein the anticancer gene product is a prodrug converting enzyme.

97. The method of claim 60, wherein the adenovirus vector is an Ad1, Ad2, Ad5 or Ad6 vector.

98. The method of claim 60, wherein the adenovirus vector is administered to the tumor by injection of vector intravenously or intrathecally.

99. The method of claim 60, wherein the adenovirus vector is administered to the tumor by direct injection of the tumor.

100. The method of claim 60, wherein the patient is passively immunized.